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CLARK & ELBING LLP
101 FEDERAL STREET
BOSTON, MA 02110

EXAMINER
PORTNER, VIRGINIA ALLEN

ART UNIT	PAPER NUMBER
1645	18

DATE MAILED: 08/08/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/848,909	Collier et al
Examiner	**Art Unit**
Portner	1645

-- The MAILING DATE of this communication appears on the cover sheet with th c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 12, 2003*.

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-4, 6-8, 12-20, 29-31, 33-35, and 40-51* is/are pending in the application.

4a) Of the above, claim(s) *43-44,48-49,50a-g,l-q; 51 d, f-g,i-j* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-4, 12-20, 29-31, 33-35, 40-42, 45-47, 50, 51, and 688* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☒ Claims *1-4,6-8,12-20.29-31.33-35.40-51* are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

New claims 40-51 have been added.

Claims 5, 9-11, 21-28, 32 and 36-39 have been canceled.

Claims 1,4,6,12,19-20, 30-31 and 33-35 have been amended.

Claims 1-4, 6-8, 12-20, 29-31, 33-35 and 40-51 are pending.

Claims 43-44, 48-49, 50a),b),c),d),e),f),g), I),m),n),p),q); 51d),f)g)I) and j) are withdrawn from consideration.

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restriction

2. Newly submitted claims 43-44, 48-49, 50a),b),c),d),e),f),g), I),m),n),p),q); 51d),f)g)I) and j) are directed to an invention that is independent or distinct from the invention originally examined for the following reasons: Claims 43-44, 48-49, 50a),b),c),d),e),f),g), I),m),n),p),q); 51d),f)g)I) and j) recite specific non-elected inventions, that define independent and distinct species, and Applicant received a first action on the merits for both D425K and ΔD2L2 . Prior art was found for ΔD2L2 (species r) of originally presented claim 4), no additional species of invention were required to be searched.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 43-44, 48-49, 50a),b),c),d),e),f),g), I),m),n),p),q); 51d),f)g)I) and j)

are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Sequence Compliance

3. The instant application is now in sequence compliance.

Allowable Subject Matter

4. Claims 4 and 19 have been amended to NO longer recite the elected species directed to "D425K", which is free of the prior art of record, and therefore are no longer indicated as allowable.

5. Claims directed to a mutant anthrax protective antigen that comprises the site directed mutation of D425K would define over the prior art of record; Claims 41, 47, 50 paragraphs h), j), k), l), o); claim 51 paragraphs a), b), c), e) and h) could be allowable if amended to remove the phrase "or a corresponding mutation in a different B moiety" , removal of non-elected inventions from the claims, and amended to recite the phrase --isolated and purified--.

Response to Amendment

6. The Declaration of Dr. R. John Collier, filed on May 8, 2003 under 37 CFR 1.131 has been considered but is ineffective to overcome the WO99/42473 reference.

7. The Declaration submitted May 8, 2003 states that Dr. R. John Collier was the only contributor to the description set forth in WO99/42473 (see paragraph 3 of Declaration), but this

statement is confusing in light of paragraphs 4 and 5 that state that Erika L. Benson and Alan Finkelstein were co-inventors, and contributed to point mutations in anthrax protective antigen.

It is the position of the examiner that the Declaration submitted May 8, 2003, provided by Dr. R. John Collier, does not clearly state that a mutation at the PA63 D2L2 loop (see WO99/42473, claim 5) was invented by him alone, nor is it clear what point mutations were invented by the combination of two or more inventors. Dr. R. John Collier did not clearly state that the additional two inventors were not inventors, but referred to them as "co-inventors". The record is not clear as to which point mutations the additional inventors contributed, and what Dr. Collier solely invented.

Claims that comprise a mutation in the PA63 D2L2 Loop are encompassed by amended and new claims 1-4, 6-8, 12-19, 29,31,33-35, 42, 45-46, especially claims 20, 30. The prior art rejection under 35 U.S.C. 102(a) is maintained for reasons of record, the record clarified and the Declaration found effective.

Rejections Withdrawn

8. Claims 4 and 19 rejected under 35 U.S.C. 112, second paragraph for reciting abbreviations, in light of the amendment of these claims to no longer recite abbreviations..

9. Claim 4 rejected under 35 U.S.C. 112, second paragraph, for reciting the species "ΔD2L2", in light of the amendment of claim 1 to no longer exclude this species and claim 4 having been amended to no longer recite this species of invention.

10. Claim 5 rejected under 35 U.S.C. 112, second paragraph, in light of the cancellation of the claim.

11. Claim 19 rejected under 35 U.S.C. 112, second paragraph or reciting the species "ΔD2L2", in light of the amendment of claim 12 to no longer exclude this species and claim 19 having been amended to no longer recite this species of invention.

12. Claim 20 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "at least 5 amino acids of the D2L2 loop", in light of the claim having been amended to recite the phrase -- further comprising--.
13. Claim 30 (renumbered) rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "a deletion of amino acids 302-325 of the D2L2 Loop" in light of the amendment of claim 12 to no longer exclude this species and the claim having been amended to recite the phrase -- further comprising--.
14. Claims 31, 34 and 35 rejected under 35 U.S.C. 112, second paragraph for reciting the phrase "if said B moiety is anthrax protective antigen", in light of the deletion of this phrase from the claims.

Rejections Maintained

15. Claims 1, 6, 12, 33 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-6, and 7 of U.S. Patent No. 6,455,673. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed species anticipates the instantly claimed genus, wherein the allowed species evidences specific mutations in the receptor binding moiety of a binary A-B toxin; the allowed toxins being moieties evidencing less affinity for sensitive cell than the wild-type toxin (see US Pat. 6,455, 673, col. 2, lines 34-40 and lines 14-35).
16. Claims 1, 6, 8, 12, 15, 33 rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13, and 23-27 of U.S. Patent No. 5,917,017. Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed species anticipates the instantly claimed genus, wherein the allowed species evidences specific mutations in the receptor binding moiety of a binary A-B toxin; the allowed toxins being moieties evidencing less affinity for sensitive cell than the wild-type toxin, wherein a claimed species comprises a deletion of amino acids 379-535 which includes the deletion of a D2L2 Loop. The allowed species anticipates the instantly claimed genus.
17. Claims 1-4,6-8, 12-20, 29-31, 33-35, 40-41, 47,50-51 sub-paragraphs h) and c) respectively, ("or a corresponding mutation in a different B moiety") rejected under 35 U.S.C. 112, first paragraph (written description), as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing, for reasons of record and arguments set forth below.

18. Claims 6-8, 33-35, and new claims 42,45-47 are rejected under 35 U.S.C. 112, first paragraph, (SCOPE, vaccine) because the specification, while being enabling for the production and use of an mutant anthrax toxin for induction of an immune response, as well as specific site directed mutants of PA antigen (PA63) for the induction of a protective immune response but, does not reasonably provide enablement for the use of any mutant toxin (protein or polypeptide) as a pharmaceutical composition (vaccine). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims, for reasons of record and arguments set forth below.
19. Claims 1, 6, 8, 12, 15 and 33 rejected under 35 U.S.C. 102(e) as being anticipated by **Collier et al** (US Pat. 5,917,017) filing date June 8, 1994), for reasons of record in paper number 14, paragraph 16.
20.Claims 1-4, 6-8, 12,13, 15, 18-20, 29-31, 33-35, 42, 45-46 rejected under 35 U.S.C. 102(e) as being anticipated **Cirino et al** (US Pat. 6,329,156, filing date March 22, 1999), for reasons of record in paper number 14, paragraph 17.
21.Claims 1, 3, 6, 8, 12, 33, under 35 U.S.C. 102(b) as being anticipated by **Johnson et al** (US Pat. 5,792,458), for reasons of record in paper number 14, paragraph 18
22. Claims 1-4, 6-8, 12-18, 31, 42-43 (chymotrypsin nicked PA, page 29041, col. 1) under 35 U.S.C. 102(b) as being anticipated by **Singh, Y et** al (1994, J. Biological Chemistry, Vol. 269) for reasons of record in # 14, paragraph 19.
23. Claims 1-4, 6-8, 12-19, 29,31, 33-35,42,45-46 rejected under 35 U.S.C. 102(b) as being anticipated by **Miller et al** (abstract 712-M, submitted by Applicant in US PTO-1449) for reasons of record in paper number 14, paragraph 20.
24. Amended and new claims 1-4, 6-8, 12-20, 29-31,33-35, 42, 45-46 are rejected under 35 U.S.C. 102(a) as being anticipated by **Collier et al** (different inventive entity; WO99/42473; submitted by Applicant in US PTO-1449), for reasons of record in paper number 14, paragraph 21, and arguments set forth herein.

Response to Arguments

25. The rejection of claims 1, 6, 12, 33 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 4-6, and 7 of U.S. Patent No. 6,455,673 is traversed on the grounds that "neither cited patent teaches or suggests all of the claim limitations of the present application, as is required for obviousness and anticipation determinations" and concludes that " the Office Action does not make clear why "a person of ordinary skill in the art would conclude that the invention defined in the claim at issue is an obvious variation of the invention defined in a claim" of either the '673 patent or the '017 patent."

26. It is the position of the examiner that claims 1, 4-7 of U.S. Patent No. 6,455,673 are directed to species of invention that comprises a mutant B-moiety, of a binary A-B toxin (see claims, the R domain and T domains are functional portions of the B-moiety, wherein the mutations are in the B-moiety (see col. 1, lines 29-39); the allowed toxin B-moieties (combination of mutant R and T domains) evidence less affinity for sensitive cell than the wild-type toxin (see US Pat. 6,455, 673, col. 2, lines 34-40 and lines 14-35).

The instantly claimed invention is directed to a genus of B-moiety mutated toxins that are binary A-B toxins (see instantly claimed claim 1), and the allowed claims are directed to a mutant B-moiety (R and T domains are portions of the binary toxin) being that portion of the binary toxin that acts to translocate the A moiety across the membrane (see US Pat. 6,455,673, col. 1, lines 37-39). It is the position of the examiner that the instant specification at page 22, line 2, teaches diphtheria toxin to be among the toxins that are considered to be of the formate included in the genus of A-B toxins.

The allowed species of binary A-B toxin of Collier et al '673, is directed to a mutant Diphtheria toxin B-moiety, which comprises a mutation in the B moiety of an A-B toxin (see '673, column 1, lines 19-21, two subunits linked by a disulfide bond; diphtheria toxin is a binary toxin of the form A-B). The allowed species of invention set forth in US Pat. 6,455,673, anticipates the instantly claimed genus of mutant B-moieties. The instantly claimed genus is rendered obvious over the allowed species. This rejection could be obviated by filing of an effective terminal disclaimer, or amendment of the claims rejected, to recite a specific species of invention not claimed by '673.

a. Additionally an allowed claimed is not required to anticipate every embodiment claimed, or disclosed in a specification as asserted by Applicant, but is only required to anticipate

or render obvious a single claimed embodiment (a single claim) in the instant Application. Instantly amended claim 1, is required to be a mutant B-moiety of an A-B toxin that comprises any mutation that inhibits pore forming ability; the allowed species anticipates the instantly claimed invention. The obviousness type double patenting is maintained for reasons of record.

27. The obviousness type double patenting rejection of claims 1, 6, 8, 12, 15, 20, 33 (renumbered claim 32) under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-13, and 23-27 of U.S. Patent No. 5,917,017 is traversed on the grounds that "the '017 patent are silent on whether any of the mutants disclosed therein necessarily inhibit the pore-forming ability of a B-moiety".

28. It is the position of the examiner that the instant specification at page 22, line 2, teaches diphtheria toxin to be among the toxins that are considered A-B toxins. The claimed B-moiety of Collier '017, is a mutant B-moiety that "lacks the segment between amino acids 379-535, inclusively, of wild type diphtheria toxin (see claim 4, '017). The recited range of amino acids in claim 4 of '017, is at the C-terminal end of the mutant B-moiety which is associated with cell receptor binding, which is an essential step prior to translocation into the cell (see col. 1, lines 35-40); when this functional domain of the B-moiety is lacking in the claimed invention of '017, the ability to translocate is inhibited. The allowed claims recite a species of the instantly claimed genus of mutant B-moieties that lack pore forming ability.

Although the conflicting claims are not identical, they are not patentably distinct from each other because the allowed species anticipates the instantly claimed genus, wherein the allowed species evidences specific mutations in the receptor binding moiety of a binary A-B toxin; the allowed toxins being moieties evidencing less affinity for sensitive cell than the wild-type toxin,

wherein a claimed species comprises a deletion of amino acids 379-535 which includes the deletion of a D2L2 Loop. The allowed species anticipates the instantly claimed genus and renders obvious the instantly claimed genus of mutant B-moieties.

29. The rejection of 1-4,6-8, 12-20, 29-31, 33-35, 40-41, 47,50-51(sub-paragraphs h) and c) elected species under examination and recite ("or a corresponding mutation in a different B moiety")) under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant specification does not contain a written description of the invention in such full, clear, concise, and exact terms or in sufficient detail that one skilled in the art can reasonably conclude that applicant had possession of the claimed invention at the time of filing is traversed on the grounds that the instant specification:

a. Applicant provided detailed structures of SEQ ID NO 1-18.

30. It is the position of the examiner that upon consideration of SEQ ID Nos 1-18, it was noted that the SEQ ID NOs are only Bacillus anthraxes sequences; these sequences do not provide support for the genus of claimed mutant B-moieties from corresponding toxins from other sources.

31. Applicant asserts that Table 6 provides support on where mutations in Clostridium difficile, C.perfringens, C.spiroforme, C.botulinum toxin and B.cereus toxins can be mutated.

32. It is the position of the examiner that while the instant specification provides support for specific site directed mutations at specific locations shown in Table 6 for specific Clostridial toxins and a second Bacillus species (cereus), along with the disclosure for Bacillus anthraxes, at pages 21-22, the specification suggests that "other toxins, such as alpha hemolysin from Staphylococcus, aerolysin from Aeromonas hydrophila, alpha toxin from Clostridium septicum, cytotoxin from Pseudomonas aeruginosa, hetero-oligomeric toxins (A-B5 toxins) or in the B

moieties of tetanus" or "diphtheria toxins", as well as "other oligomeric virulence factors, ranging from toxins to adhesins" are defined to be included in the scope of the genus claims now recited.

No mutant B moieties for alpha hemolysin from Staphylococcus, aerolysin from Aeromonas hydrophila, alpha toxin from Clostridium septicum, cytotoxin from Pseudomonas aeruginosa, hetero-oligomeric toxins (A-B5 toxins) or in the B moieties of tetanus" or "diphtheria toxins", as well as "other oligomeric virulence factors, ranging from toxins to adhesins (paragraph bridging pages 21-22 of the instant specification)" are specifically described in the instant specification. While Applicant as provided written descriptive support for Clostridial and Bacillus mutant B-moieties in Table 6, and SEQ ID No 1-18, the specification has not described mutant B-moieties from Staphylococcus, Aeromonas, hetero-oligomeric toxins, and the genus of proteins known as toxins and oligomeric adhesins, and B-moieties from a "corresponding" toxin B-moiety; the claimed products have not been described by structure correlated with function.

The narrative at the top of page 22 states :

"Additionally, these results underscore the possibility of identifying dominant negative forms of a number of other oligomeric virulence factors, ranging from toxins to adhesins". Clearly this statement shows that Applicant was not in possession of mutant B-moieties for the instantly claimed genus based upon the definition provided at page 21, lines 22-26 through page 22, lines 1-4.

The examiner agrees that Applicant was in possession of a screen to identify mutant B-moieties for the recited functional characteristics, but was is under examination is a product claim and not a method of screening . The claimed genus of mutant B-moieties are claimed based upon function, as well as what the mutant B-moieties are not. The claims recite a negative structural limitation (independent claims), rather than what the mutant B-moiety is structurally (see for example, claim 1).

33. Examples 6, 7, 9 and Tables 3-5 are cited as support for written description of the instantly claimed invention of claim 12.

34. It is the position of the examiner that the support to which Applicant directs the examiner shows mutant B-moieties of Bacillus anthraxes, protective antigen, site directed mutants, that do not provide written descriptive support over the entire scope of the claimed invention directed to any mutant B-moiety with the recited functional ability, which is not defined structurally. The claimed invention of claim 12 is functionally defined, as well as what structures it does not encompass; the genus of inventions is not structurally defined by any specific amino acid sequence through the positive recitation of an amino acid sequence.

a.The rejection under 35 U.S.C. 112, first paragraph (scope of written description) is maintained for reasons of record in paper number 14, paragraph 12.

35. The scope of enablement rejection of Claims 6-8, 33-35, and new claims 42,45-47 are rejected under 35 U.S.C. 112, first paragraph, (SCOPE, vaccine) because the specification, while being enabling for the production and use of an mutant anthrax toxin for induction of an immune response, as well as specific site directed mutants of PA antigen (PA63) for the induction of a protective immune response but, does not reasonably provide enablement for the use of any mutant toxin (protein or polypeptide) as a pharmaceutical composition (vaccine). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims is traversed on the grounds that:

a. The instant specification has provided "in the form of a working example, that the claimed B moiety vaccine compositions induce a protective immune response in vaccinated rates that enables rats to survive injection with lethal doses of anthrax toxin" and asserts that "the specification does enable the claimed invention";

b. Asserts that no evidence supporting the rejection was been provided;

c. Asserts that is no reason to doubt the objective truth of Applicant's specification;

d. Asserts that screening mutant moieties in standard assay to determine whether they inhibit pore forming ability are taught in the specification; and

e. Concludes the claimed invention would induce protective immunity in a vaccinated animal.

36. It is the position of the examiner that the rejection made of record was a SCOPE of enablement, and at no time did the examiner state that the disclosed compositions would not serve as immunogenic compositions for the induction of neutralizing antibodies.

The scope of enablement was made with respect to the "any fragment thereof "mutant B-moieties protecting against any pathogen that produces a B-moiety, as well as "any mutant B-moiety of PA antigen". The claimed inventions of the independent claims are not limited to any specific size B-moiety, and include fragments of the B-moiety that are not required to induce an immune response, no less a protective immune response. No protective fragments that are epitopes have been disclosed. The challenge compositions were not viable bacteria, but biologically active anthrax toxin. Applicant's arguments are not commensurate in scope with the claimed invention which is directed to vaccines directed against entire microorganisms and not just able to inhibit a biologically active toxin.

Contrary to Applicant's assertion that no evidence supporting the rejection was been provided, the examiner cited two references to provide evidence that a highly immunogenic proteins expected to protect against infection and disease, may not or did not induce a protective immune response (see Boslego et al and Ellis et al). Additional evidence was cited for compositions that comprise B-moieties, specifically Cherry (1999) that teach a pertussis based vaccine failed (see page 22, Office Action, paper number 14). Sellman et al and Guttman et al were sited to show negative side effects induced by mutants of anthrax protective antigen or an anthrax vaccine, thus not producing the desired therapeutic effect.

Contrary to Applicant's assertion that the examiner questions the objective truth of Applicant's specification, the examiner set forth a scope of enablement rejection over claims directed to vaccines. Claims directed to immunogenic or antigenic compositions would obviate this rejection.

Applicant's assertion that screening mutant moieties in standard assay to determine whether they inhibit pore forming ability are taught in the specification was not the complete basis of the scope of enablement rejection. The functionality of the recited compositions was not the only point raised with respect to the claimed vaccine compositions. While a composition that comprises a mutant B-moiety could be screened to find out if the mutation inhibits formation of pores, the indication of a protective immune response against challenge with a viable, virulent Bacillus anthraxes bacterium in vivo, is clearly a different matter. The in vitro screening methods have not been shown to directly correlate with protection against infection and disease caused by a by Bacillus anthraxes bacterium in vivo. The in vivo method used in the specification evaluated the mutant anthrax B-moiety compositions for their ability to inhibit pore formation with un-mutated protective antigen containing compositions; this is not a challenge composition with a viable bacteria.

Vaccines are not predictable in the art of therapeutics. Evidence was provided to show unpredictability of highly immunogenic compositions to not protect against pathogen challenge (Boslego et al). The scope of the claims reaches through to mutant B-moieties that are not described or disclosed in the instant specification, and are enabled for compositions that are immunogenic but not vaccines for any B-moiety producing pathogen. The rejection is maintained for reasons of record in paper number 14, paragraph 13.

37. The rejection of claims 1, 6, 8, 12, 15 and 33 rejected under 35 U.S.C. 102(e) as being anticipated by **Collier et al** (US Pat. 5,917,017)filing date June 8, 1994) is asserted to not anticipate the instantly claimed invention by stating:

a.diphtheria toxin is not a binary A-B toxin as defined by "a "pore-forming A-B toxin in which the A and B moieties of the pore-forming toxin inhabit separate proteins, and interact during the intoxication of host cells." and concludes that diphtheria toxin consists of a single protein that is excreted from a bacterial cell after synthesis and therefore is not a binary toxin. 38. It is the position of the examiner that the instant specification at page 22, line 2, teaches diphtheria toxin to be among the toxins that are considered A-B toxins. Applicant should review the toxins listed at pages 21-22 prior to arguing against the teachings of the instant specification.

Collier et al disclose the claimed invention directed to a B moiety of a pore-forming binary A-B toxin (see '017, column 1, lines 12-40), which by Applicant's own definition at page 22, is an A-B toxin included within the scope of the genus claims.

Diphtheria toxin is defined to comprise two moieties, an A-moiety and a B-moiety (see column 1, lines 16-17). Collier et al, '017, defines diphtheria toxin as an A-B moiety containing toxin. Applicant's arguments do not address the specific disclosure of Diphtheria toxin as an A-B moiety toxin provided by Collier et al, '017.

The B-moiety of Diphtheria toxin comprises more than one domain, one domain binds to the host cell receptor, and the other domain functions in forming a pore (translocation across the host cell membrane; see Collier et al, column 1, lines 36-37).

With respect to Applicant arguments directed to a single protein, it is the position of the examiner that diphtheria toxin comprises two moieties, which are cleaved one from the other at the appropriate time to cause intoxication of the host cell (see col. 1, line 16 "disulfide bond"; col. 1, lines 37-38 "releasing catalytically active fragment A into the cytosol of the cell").

Therefore Diphtheria toxin comprises first and second moieties, referred to as A-B fragments, and are moieties; each moiety evidencing the recited claimed functional characteristics of the instant invention, and the claimed and disclosed B-moieties of Collier et al '017, comprise a mutation that inhibits its pore-forming ability (see all claims of '017; col. 2, lines 29-44). Applicant's Representative has not distinguished the instantly claimed genus claim from the

embodiments disclosed by Collier et al, '017. The reference inherently anticipates the instantly claimed invention for reasons of record in paper number 14, paragraph 16.

39. The rejection of claims 1-4, 6-8, 12,13, 15, 18-20, 29-31, 33-35, 42, 45-46 under 35 U.S.C. 102(e) as being anticipated **Cirino et al** (US Pat. 6,329,156, filing date March 22, 1999), is traversed on the grounds that "the mutation in Cirino's PA32 fragment that inhibits its pore-forming ability is a mutation of Phe313, Phe314 or Asp315 (a deletion mutation of these residues in the D2L2 loop), Cirino does not teach a mutation that inhibits pore-forming ability that is not a mutation of Phe313, Phe314 or Asp315."

40. It is the position of the examiner that Applicant's arguments are not commensurate in scope with the instantly claimed invention. The negative claim limitations recited and argued are in the alternative, and only excludes single point mutations in the alternative. A mutation of the entire D2L2 loop is claimed by Applicant in claims 20 and 30, which depend indirectly from claim 12 which recites "Phe313, Phe314 **or** Asp315" mutations. Applicant's arguments are not commensurate in scope with the instantly claimed invention which includes the deletion of the D2L2 loop of PA antigen.

Additionally, the examiner would like to clarify the fact the claims also include in addition to the deletion of the entire D2L2 loop, combinations of mutations such as:

Phe313 and Phe314; or

Phe313 and Asp315; or

Phe314 and Asp315; or

Phe313, and Phe314 and Asp315. The only mutations not claimed in the amended claims are mutations at any ONE of the recited positions; the claims include combinations of mutations at the recited locations, as the point mutations are excluded in the ALTERNATIVE.

Cirino et al disclose the claimed invention directed to a B moiety of a pore-forming binary A-B toxin, wherein the B-moiety comprises a mutation that inhibits its pore-forming ability (see

col. 10, lines 59-64 and col. 10, lines 1-15, lines 17-58). The rejection is maintained for reasons of record in paper number 14, paragraph 17.

41. The rejection of claims 1, 3, 6, 8, 12, 33 under 35 U.S.C. 102(b) as being anticipated by **Johnson et al** (US Pat. 5,792,458) is traversed on the grounds that:

a.diphtheria toxin is not a binary A-B toxin as defined by a "pore-forming A-B toxin in which the A and B moieties of the pore-forming toxin inhabit separate proteins, and interact during the intoxication of host cells." and concludes that diphtheria toxin consists of a single protein that is excreted from a bacterial cell after synthesis and therefore is not a binary toxin.

42. It is the position of the examiner that the instant specification at page 22, line 2, teaches diphtheria toxin to be among the toxins that are considered A-B toxins. Applicant should review the toxins listed at pages 21-22 prior to arguing against the teachings of the instant specification.

Johnson et al disclose the claimed invention directed to a B moiety of a pore-forming binary A-B toxin (see Figure 5, A chain (A-moiety) and B chain (B-moiety), thus defining Diphtheria toxin to comprise two moieties, an A-moiety and a B-moiety. The B moiety of the A-B toxin, comprises two domains, one for receptor binding and the other being for translocation (pore forming activity).

Johnson et al disclose a B moiety of a pore-forming binary A-B toxin, wherein the B-moiety comprises a mutation that inhibits its pore-forming ability, because the B-moiety does not form a pore prior to host cell receptor binding (see col. 6, lines 61-67; figures and all claims).

Toxicity is caused by the A-moiety that evidences separate enzymatic activity from the functional activity of the B-moiety. The mutant B-moiety of Johnson et al anticipates the instantly claimed invention, for reasons of record, in paper number 14, paragraph 18.

43. The rejection of claims 1-4, 6-8, 12-18, 31, 42-43 under 35 U.S.C. 102(b) as being anticipated by **Singh,** Y et al (1994, J. Biological Chemistry, Vol. 269) is traversed on the grounds that:

a. The claims recite the phrase "not a mutation of Phe313, Phe314 or Asp315 of anthrax protective antigen; and

b. the reference does not teach a mutation that inhibits pore-forming ability that is not a mutation of Phe313, Phe314 or Asp315.

44. It is the position of the examiner that Applicant claims mutations of the D2L2 loop of anthrax protective antigen which includes the mutation of amino acids that include Phe313, Phe314 and Asp315; Applicant arguments and reading of the claims as amended is not commensurate in scope with the instantly claimed invention.

Additionally, the mutations excluded from the claims is any of the single site directed mutations of Phe313, Phe314 or Asp315, and combinations of mutations of Phe313, Phe314 and Asp315 are included within the scope of the claimed invention; this reading of the claims is included in Applicant's claim to mutant anthrax protective antigen B-moieties that evidence the deletion of the D2L2 loop which includes amino acids 313-315, specifically amino acids 302-325.

Finally, Singh et al disclose double and triple mutants in this region. The double mutant delta 313 and 314 (see Figure 1), is a species of anthrax protective antigen that lacks toxicity (see figure 1, page 29041) and the triple mutant (AAA) is an anthrax protective antigen that evidences reduced toxicity (see page 29041, col. 1, paragraph 3, bottom of paragraph). Singh, Y et al (Nov. 1994) discloses the claimed invention directed to a mutant B-moiety of a pore forming binary A-B toxin, wherein the B moiety comprises a mutation that inhibits pore-forming ability, for reasons of record in paper number 14, paragraph 19.

45. The rejection of claims 1-4, 6-8, 12-19, 29,31, 33-35,42,45-46 under 35 U.S.C. 102(b) as being anticipated by **Miller et al** (abstract 712-M, submitted by Applicant in US PTO-1449) is traversed on the grounds that:

a. The claims recite the phrase "not a mutation of Phe313, Phe314 or Asp315 of anthrax protective antigen; and

b. the reference does not teach a mutation that inhibits pore-forming ability that is not a mutation of Phe313, Phe314 or Asp315.

46. It is the position of the examiner that Applicant claims mutations of the D2L2 loop of anthrax protective antigen which includes the mutation of amino acids that include Phe313, Phe314 and Asp315; Applicant arguments and reading of the claims as amended is not commensurate in scope with the instantly claimed invention.

Miller et al disclose the claimed invention directed to a B moiety of a pore-forming binary A-B toxin, wherein the B-moiety comprises a mutation that inhibits its pore-forming ability (see entire abstract), wherein the resultant B moiety was oligomerized, deficient in the ability to permeable membranes, and to translate the enzymatic moieties of anthrax toxin.

Applicant requests evidence that the mutant B-moiety would evidence the asserted inherent characteristic. It is the position of the examiner that no evidence has been made of record by Applicant to show that the mutant of Miller does not have the recited functional characteristic; and Applicant claims the disclosed embodiment of Miller to evidence the recited functional characteristic. Applicant's claimed invention provides evidence that the B-moiety has the recited functional characteristic. The examiner cited case law, specifically Atlas Powder Co V IRECA to show that a known composition is not patentable based upon the discovery of a new functional characteristic of the composition. The rejection is maintained for reasons of record in paper number 14, paragraph 20.

47. The rejection of claims 1-3, 6-8, 12-18, 29, 31, 33-35 (renumbered claims 28, 30, 32-34) are rejected under 35 U.S.C. 102(a) as being anticipated by Collier et al (different inventive entity; **WO99/42473**; submitted by Applicant in US PTO-1449), is traversed on the grounds that the Declaration submitted May 8, 2003 states that Erika L. Benson and Alan Finkelstein contributed to point mutations in anthrax protective antigen that are not claimed in the instant Application.
48. It is the position of the examiner that the Declaration submitted May 8, 2003, provided by Dr. R. John Collier, does not clearly state that a mutation at the PA63 D2L2 loop (see WO99/42473, claim 5) was invented by him alone. This embodiment is encompassed by amended claims 1-4, 6-8, 12-19, 29,31,33-35, 42-46, especially claims 20, 30. The rejection is maintained for reasons of record, and until the record is clarified with respect to what embodiments of point mutations the Declaration is specifically referring; the Declaration was found to be ineffective.

Collier et al disclose the claimed invention directed to a B moiety of a pore-forming binary A-B toxin, wherein the B-moiety comprises a mutation that inhibits its pore-forming ability (see entire document and claims), wherein the resultant B moiety was an anthrax protective antigen mutant toxin or the PA63 domain. The moiety was formulated into a prophylactic and immunogenic composition (see page 23, lines 26-28; page 4, lines 17-20). The purified mutant was gel filtered and combined with 150 mM NaCl, a pharmaceutically acceptable carrier (see page 12, lines 17-18). The reference inherently anticipates the instantly claimed invention.

New Claims/New Claim Limitations/New Grounds of Rejection

Claim Rejections - 35 U.S.C. § 101

49. Claims 1-4, 12-20, 29, 40-41, 50-51 are not isolated and purified, and Price et al (Journal of Bacteriology, 1999) teaches that naturally occurring mutants exist in nature; the claimed invention is directed to non-statutory subject matter. This rejection could be obviated by amending the claims to recite --isolated and purified-- to show the "hand of man".

Claim Rejections - 35 USC § 112

50. Claims 1, 3, 6,8,12,15-18,33,40-41, 47, 50-51(subparagraphs directed to the elected invention) are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claimed invention includes those B-moieties which evidence mutations defined by the phrase "or corresponding residues in B moieties". The reference B-moiety of a pore forming toxin of the binary form of A-B subunits need not be anthrax protective antigen, as the claims only require the invention NOT to be the recited specifies of anthrax protective toxin, and in the case of claims 40-41, 47 and 50-51, where the reference molecule is anthrax protective antigen, what the corresponding B-moiety sequences encompassed by the claims are have not been described by structure correlated with function and therefore have not been described. The claimed invention of claims must only evidence the functional characteristic of evidencing reduced pore forming ability, the mutation being one that is either a chemical or physical mutation.

The instant specification has not enabled one of skill in the art to make and use mutant B-moieties in "corresponding residues in B moieties" because the claimed moieties are only functionally defined. What the chemical structures of the claimed "corresponding residues in B-moieties" of claims 1, 3, 6,8,12,15-18,33, have not been claimed based upon any specific sequence that must correspondingly be mutated and what has not been described can not be made or used. The embodiment encompassed by the phrase "or corresponding residues in B-moieties" relative to a reference antigen, but have not been described by what the corresponding residues are, also have not been described; these embodiments have not been enabled.

51. Claims 1, 12, 30, 33, 40-41, and 47 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 12, 30, 33, 40-41, and 47 recite the phrase "or corresponding residues in B moieties", without distinguishing the"B-moiety" from the "corresponding" B-moiety. How are the B-moiety and the corresponding B-moiety the same or different from each other? The invention is not distinctly claimed.

Claims 1, 12, 30, 33, 40-41, and 47 recite the phrases directed to a mutation present in "corresponding residues in B moieties" or "a corresponding mutation in a different B moiety"; what does the mutation correspond to without a reference sequence to correspond? How does it correspond, directly or indirectly? How many mutations are present in the corresponding B-moiety without any specific reference mutation being required. Correspondence to any B-moiety that differs in amino acid sequence, size and organization does not directly correspond to anthrax protective antigen. The invention is not distinctly claimed based upon the recitation of the cited phrase above, because no clear point of reference is set forth in the claims that provide a definite point of determining what that claim mutant B-moieties are. The meets and bounds of the claim are unclear, as all B-moieties evidence differ structural amino acid sequence, and different sizes and would therefore evidence different correspondences relative to anthrax protective antigen. What the recited correspondence is, is not distinctly claimed absent a defined structural correspondence, coupled with guidance and teaching as to what the corresponding mutant B-moieties would be.

Claim 8 recites the phrase "is inactivated by chemical or physical means"; a process step that does not clearly define any specific structural change. Is the physical means the mutation recited in claim 6? How does the physical means of claim 8 differ from the mutation(s) of claim 6 from which claim 8 depends? Is inactivation different from a mutation that inhibits pore forming ability ? Additionally, the word "inactivated" lacks antecedent basis in claim 6.

Claims 14-18 recite the phrase "having the ability" or "lacks the ability"; how do the recited abilities further limit the abilities of amended independent claim 12, from the B-moieties in claims 14-18? The mutant B-moiety of claim 12 has all of the recited abilities of the dependent

claims. How are claims 14-18 further limiting of and distinguished from the B-moiety of claim 12?

Conclusion

52. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

53. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ginny Portner whose telephone number is (703)308-7543. The examiner can normally be reached on Monday through Friday from 7:30 AM to 5:00 PM except for the first Friday of each two week period.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909. The fax phone number for this group is (703) 308-4242.

The Group and/or Art Unit location of your application in the PTO will be Group Art Unit 1645. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to this Art Unit.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Vgp
August 4, 2003

LYNETTE R. F. SMITH
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600